

Review

Recent Insights into Hippocampal Dysfunction and Neuroplasticity in Sleep Disorders: An Update from Preclinical Studies

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Abstract

Sleep disorders are prevalent neurological conditions linked to neurocognitive impairments. Understanding the neuroplasticity changes in the hippocampus, which plays a central role in regulating neurocognitive function, is crucial in the context of sleep disorders. However, research on neurodegenerative disorders and the influence of sleep disorders on hippocampal neuroplasticity remains largely unclear. Therefore, this review aims to highlight the latest advancements regarding hippocampal neuroplasticity and functional changes during sleep disorders, drawing insights from clinical and preclinical research involving sleep-deprived animal models. These articles were gathered through comprehensive literature searches across databases, including Google Scholar, PubMed, Web of Science, and Scopus. Maternal sleep deprivation has been observed to cause neurocognitive impairment in offspring, along with changes in protein expression levels associated with neuroplasticity. Similarly, sleep deprivation in adult mice has been shown to affect several cognitive functions and fear extinction without influencing the acquisition of fear conditioning. While mechanistic research on neurocognitive dysfunction induced by maternal and adult sleep deprivation is limited, it suggests the involvement of several signaling pathways, including neurotrophic factors, synaptic proteins, and inflammatory molecules, which are triggered by sleep deprivation. Further studies are needed to clarify the mechanistic pathways underlying hippocampal dysfunction and synaptic alterations associated with sleep disturbances.

Keywords: animal model; cognition; hippocampus; sleep disorder; synaptic plasticity

1. Introduction

Sleep is crucial in maintaining overall health and well-being. Deprivation of sleep is intricately linked to several challenges across various body systems, including the endocrine, metabolic, and neurological domains [1–3]. The importance of a proper and adequate sleep in normal brain development and function has been considerably explored [4,5]. Sleep dynamics can profoundly influence brain development throughout an individual's lifespan and are involved in neurodegeneration [6]. During early life, which is characterized by rapid developmental changes, sleep is a fundamental brain activity that crucially contributes to healthy cognitive and psychosocial development [7]. Sleep disorders manifest in different forms, ranging from complaints of inadequate sleep to perceived excessive or abnormal movements during sleep [8,9]. Chronic sleep disturbances are linked to neurobehavioral deficits and physiological abnormalities, often resulting in psychiatric conditions such as cognitive dysfunction and depression [10,11]. For instance, research findings suggest that 40% and 47% of individuals experiencing insomnia and excessive sleepiness also exhibit neuropsychiatric disorders, respectively [12]. Furthermore, disturbed nocturnal sleep patterns are common among individuals experiencing depression, as revealed in clinical and epidemiological studies, where approximately 83% of patients with depression report at least

one symptom of insomnia [13]. Therefore, sleep disorders, including insomnia and abnormal sleep patterns, frequently co-occur with neuropsychiatric conditions such as cognitive impairment and emotional dysregulation, highlighting the intricate interplay between sleep quality and mental well-being.

The hippocampus, extensively explored for its diverse roles in learning, cognition, memory storage, depression, and anxiety, serves as a focal point of investigation among other brain regions. Furthermore, it serves as a focal pivotal area for exploring the pathophysiology of various neurological diseases characterized by functional alterations, encompassing neurodegenerative [14,15] and neuroinflammatory diseases [16,17], traumatic brain injuries (TBI) [18], and sleep disorders [19]. Moreover, the hippocampus has received significant attention in studies investigating changes in neuroplasticity, particularly concerning neurological insults such as neurodegenerative diseases [15] and sleep disorders [19]. Previous research has explored hippocampal neuroplasticity based on neurodegenerative disorders [15]. However, the influence of sleep disorders on hippocampal neuroplasticity remains largely unclear.

Sleep architecture comprises two distinct stages: rapid-eye-movement (REM) (also known as paradoxical sleep) and non-REM (NREM) sleep (encompasses deep slow-wave sleep). Electroencephalogram (EEG) record-



Table 1. Classification of sleep disorders based on ICSD-3 with typical examples and symptoms.

ICSD-3 major category	Typical symptoms
Insomnia	Difficulty initiating and maintaining sleep
Sleep-related breathing disorder	Excessive daytime sleepiness
Central disorder of hypersomnolence	Excessive daytime sleepiness, cataplexy (with narcolepsy)
Parasomnia	Nocturnal movements, sleepwalking
Sleep-related movement disorder	Urge to move legs, difficulty initiating sleep
Circadian rhythm sleep disorder	Difficulty initiating and maintaining sleep, early awakening, and excessive daytime sleepiness

Abbreviations: ICSD-3, international classification of sleep disorders-third edition.

ings facilitate the determination and quantification of these stages [20]. REM and NREM sleep stages exhibit distinct oscillatory rhythms in the EEG. Theta rhythms characterize REM sleep, while NREM sleep features slow waves, spindles, and sharp wave ripples. Certain EEG patterns, such as theta oscillations in REM sleep and high-frequency sharp wave ripples in NREM sleep, involve approximately 10–18% of hippocampal neurons [21]. These EEG rhythms are proposed to play crucial roles in memory consolidation [22–24] and in transmitting information from the hippocampus to the cortex and other brain regions [25,26]. Moreover, the hippocampus contains a neurogenic niche in adults, contributing to its neuroplasticity capacity. Neurogenesis—a complex process—is implicated in hippocampal neuroplasticity changes observed across various neurological conditions, including sleep disorders. The hippocampus serves multiple higher-level functions, with newly formed neurons potentially integrating into processes such as mood regulation [27] and learning and memory [28]. The influence of sleep on adult hippocampal neurogenesis has long been recognized. For example, total sleep deprivation ≥ 48 h consistently reduces the basal rate of cell proliferation in the dentate gyrus by 30–80% [29]. Overall, sleep disorders clearly affect hippocampal plasticity from multiple perspectives.

Therefore, this review aims to synthesize articles predominantly focusing on hippocampal neuroplasticity based on sleep disorders. By examining clinical and preclinical studies that focused on sleep dysregulation, these findings could shed light on potential therapeutic strategies for regulating aberrant hippocampal neuroplasticity in neurodegenerative diseases. Additionally, it seeks to identify existing gaps in comprehending hippocampal neuroplasticity within the context of neurodegenerative disorders, thereby serving as a reference point for future research endeavors.

2. Sleep Disorders: A Comprehensive Overview

Sleep, a dynamic and multifaceted behavioral process, can experience disruptions at different stages. The International Classification of Sleep Disorders-Third Edition (ICSD-3) outlines six primary categories [30,31]: insomnias, sleep-related breathing disorders, central hypersomnolence disorders, parasomnias, sleep-related movement disorders, and circadian rhythm sleep disorders (Table 1).

2.1 Insomnia

Insomnia is characterized by difficulty initiating or maintaining sleep. It results in significant daytime repercussions, including impaired functionality, decreased work performance, social withdrawal, and fatigue [32,33]. Individuals experiencing insomnia struggle to sleep even when provided sufficient opportunity to do so in a conducive environment. It frequently coexists with other conditions, such as depression, neurological disorders, cardiovascular disease, diabetes, respiratory issues, gastrointestinal complications, and cancer [32]. Moreover, insomnia elevates the risk of developing neuropsychiatric disorders and cardiovascular disease. However, an effective treatment strategy can enhance cardiovascular and mental health outcomes [34,35]. Research findings suggest that approximately 10% of adults experience insomnia, while up to 20% of patients in primary care report symptoms leading to functional impairment and reduced productivity [33,36].

Studies on the hippocampal structure in insomnia have yielded varied findings. Some indicate diminished hippocampal volume among patients with insomnia [37,38]. In contrast, others demonstrate negative associations between hippocampal volume and subjective sleep quality [39]. Conversely, other studies have reported no differences in hippocampal volume between individuals with insomnia and control groups [40,41]. Different subtypes of insomnia may plausibly demonstrate distinct hippocampal connectivity patterns. We consider it crucial and timely to address these findings in our review to enhance our understanding of the hippocampal involvement in insomnia.

2.2 Sleep-Related Breathing Disorder

The classification system of the American Academy of Sleep Medicine categorizes sleep-related breathing disorders as obstructive apnea, central sleep apnea, and sleep-related hypoventilation [30,42]. These nocturnal events can raise pulmonary arterial pressure during sleep and while awake [43]. However, the treatment approach for these diverse disorders often follows similar principles. Typically, alleviating the sleep-related breathing disorder involves addressing underlying medical conditions or adjusting medications.

Sleep-related breathing disorders are linked to neural injury that influences many physiological systems, including sensing chemoreception and airflow, respiratory musculature, timing circuitry for breathing pattern coordination, and blood pressure mechanisms integrated with respiration [44]. Sleep-related breathing disorders exert complex and poorly understood effects on cognition and daytime memory, involving the hippocampus. For instance, obstructive sleep apnea, observed in adults and children, is frequently associated with different levels of mood dysregulation and cognitive deficits [45]. Clinical cases have revealed decreased neural metabolites in the hippocampus and frontal cortex, leading to impaired memory, learning, and executive functions [45,46]. Untreated neural, cognitive, and daytime functional impairments can lead to severe downstream consequences. Improving our understanding of the cognitive effects associated with these disorders and advancing the development of more efficient diagnostic assessment tools will facilitate early intervention, thereby improving the quality of life of patients.

2.3 Central Disorder of Hypersomnolence

Central disorders of hypersomnolence encompass several marked conditions characterized by excessive daytime sleepiness stemming from pathological origin. The underlying pathophysiology of most of these disorders remains elusive. While excessive daytime sleepiness is a shared characteristic among these conditions, their classification can be further aided by considering additional clinical presentations, such as cataplexy, sleep duration, and episodic or continuous nature of symptoms [47,48].

Memory function typically remains intact in patients with central disorders of hypersomnolence, while specific subgroups may experience impairments in higher-order cognition, decision-making, and emotional processing [49]. Some patients exhibit hypermetabolism in various brain regions, including the hippocampus [50,51]. However, studies exploring the involvement of the hippocampus in central hypersomnolence disorders remain limited.

2.4 Parasomnia

Parasomnia is commonly classified according to the sleep state from which it originates: NREM and REM [30]. NREM parasomnia includes arousal disorders, such as confusional arousal, sleepwalking, and sleep terrors. These behaviors manifest when the cortex incompletely arouses from deep NREM sleep, often triggered by comorbid conditions that induce repeated arousal and/or promote sleep inertia. Alterations in the cyclic alternating pattern, a biomarker indicating arousal instability during NREM sleep, have been observed in sleepwalking and related disorders [52].

A significant feature of REM parasomnia is its higher prevalence among males [53,54]. Evidence of hippocampal involvement in REM parasomnia is clear by height-

ened theta rhythms, indicating increased hippocampal activity during REM sleep [55]. However, the involvement of the hippocampus in REM and parasomnia is complex, involving interactions with other brain regions, such as the cortex [56]. Recognizing the role of the hippocampus in REM parasomnia highlights the importance of a comprehensive investigation of its interaction with other brain regions. Such research provides vital insights for advancing our understanding and management strategies for this complex sleep disorder.

2.5 Sleep-Related Movement Disorders

Sleep-related movement disorders include various repetitive movements that frequently disturb sleep, resulting in insomnia, diminished sleep quality, fatigue, and excessive daytime sleepiness. This category encompasses conditions such as restless leg syndrome, periodic limb movement disorder, sleep-related leg cramps, sleep-related bruxism, and sleep-related rhythmic movement disorders [30,57]. Despite their clinical significance, the specific brain regions involved in these disorders remain largely elusive and, unfortunately, underexplored.

Recent magnetic resonance imaging (MRI) studies investigating restless leg syndrome have provided some insights into the structural abnormalities within the brain [58,59]. These studies revealed marked morphological alterations, particularly in the bilateral amygdala, and less pronounced changes in regions such as the hippocampus, right caudate, left globus pallidus, and left putamen. Additionally, a population-based study involving 189 individuals revealed a correlation between periodic limb movements during sleep. It reduced hippocampal and amygdala volume [60]. Cumulatively, these findings suggest the potential involvement of the hippocampus in sleep-related movement disorders. Consequently, further studies exploring the synaptic plasticity changes within the hippocampus associated with these disorders are warranted. Such investigations could provide valuable insights into the underlying mechanisms and potentially guide the development of more effective targeted treatment approaches.

2.6 Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders involve disturbance of the internal clock of the body, which regulates various physiological processes, including sleep-wake cycles [30,61]. Previous study findings have prompted discussions regarding the degree of hippocampal involvement in the circadian system [62–65]. While several reviews have presented varying perspectives on this topic [66–68], the precise nature of this relationship remains subject to ongoing investigation.

It is well-established that the circadian rhythm and REM sleep significantly influence memory consolidation, a process heavily dependent on hippocampal activity [69]. A study found that rats experiencing circadian rhythm sleep

Table 2. Overview of literature investigating sleep disorders associated with hippocampal dysfunction and neuroplasticity changes.

Animal model/clinical study	Effect on sleep/Effect of disease model on sleep	Changes in hippocampal neuroplasticity	Reference
Sleep-deprived CD-1 mice (maternal)	Induced cognitive impairment Environmental enrichment recovered cognitive function	Decreased BDNF and PSD95 Environmental enrichment recovered BDNF and PSD95 levels	[74]
Sleep-deprived CD-1 mice (maternal)	Induced depression-like behavior and learning and memory impairments Environmental enrichment improved behavioral dysfunction	Increased proinflammatory cytokines Decrease in neuroplasticity-associated proteins Environmental enrichment restored the neuroplasticity proteins	[73]
Sleep-deprived (maternal) Sprague Dawley rats		Pups born to REM sleep-deprived dams exhibited a significantly higher percentage of active sleep throughout the examination period, alongside reduced latency during postnatal days 15–21 Induced maturational delay in the sleep-wake neural networks	[75]
CD-1 mice with maternal sleep deprivation	Induced anxiety-like behavior and cognitive impairment Environmental enrichment recovered behavioral deficits	Decreased neurotrophic factors (BDNF and Syt-1) Environmental enrichment restored sleep deprivation-induced molecular changes	[72]
CD-1 mice with maternal sleep deprivation	Induced emotional and cognitive impairments Fragmented sleep deprivation exacerbated cognitive performance to a greater extent compared to continuous sleep deprivation		[71]
Sleep-deprived C57BL6 mice	Induced depression-like behavior	Reduced expression of neurotrophic factors Increased cytokines in the hippocampus	[76]
Sleep-deprived C57BL6J mice		Identified 1146 DEGs: 507 upregulated and 639 downregulated genes Upregulation was associated with RNA splicing and the nucleus Downregulation was associated with cell adhesion, dendritic localization, the synapse, and postsynaptic membrane	[82]
Sleep-deprived C57BL6J mice	Impaired object place recognition memory in young adult mice but enhances the performance in old mice		[79]
Sleep-deprived C57BL6J mice		Showed 16 common DEGs in sleep deprivation and AD mice	[83]
Sleep-deprived Wistar rats	Induced cognitive dysfunction	Triggered the elevation of hippocampal autophagy Reduced generation of endogenous H ₂ S and CBS and 3-MST expression	[80]
Sleep-deprived Sprague Dawley rats	Affected extinction of conditioned fear, but not the acquisition of fear conditioning	Inhibited hippocampal proBDNF activity rises during the circadian cycle	[81]
Sleep-deprived Wistar rats		Short period (<90 min) of selective RSR exhibited a strong REM sleep homeostatic drive Increased REM sleep homeostatic drive increased phosphorylation and activation of ERK1/2 and BDNF expression in the pedunculopontine tegmentum	[95]

Table 2. Continued.

Animal model/clinical study	Effect on sleep/Effect of disease model on sleep	Changes in hippocampal neuroplasticity	Reference
Sleep-deprived C57BL/6J mice	Affected the contextual memory, but not cued memory BDPP protective against sleep deprivation-induced contextual memory impairment	Impaired CREB activation and mTOR signaling pathways BDPP exerts a protective effect through CREB activation and mTOR signaling pathways	[77,96,97]
Sleep-deprived C57BL/6J mice	Sleep deprivation during hours ZT 2–5 after OPR training impairs long-term memory and LTP		[78]
Sleep-deprived SD rats		Enhanced IL-1 β and TNF- α expression Decreased <i>BDNF</i> mRNA levels after 5 days	[84]
Wistar and SD rats simulated shift work		Simulated night shift work in rats disrupts the pathways regulating the circadian component of the translation of mRNA in the PFC	[85]
SHR and WKY rats	CRD and hypertension reduced memory performance and novel object recognition and preference	Decreased fractional anisotropy values, the number of neurons and astrocytes and the expression of BDNF and synapsin 1 in the hippocampus Enhanced neuron and microglia degeneration, reduced hippocampal blood flow, and increased NF- κ B, caspase, NSE, and IL-6 levels	[64]
Female CBA/JRi mice		Synaptic Shank3 protein levels oscillated in the hippocampus and striatum throughout the day, correlating with serum melatonin fluctuations Physical activity impaired Shank3 α oscillation	[86]
Male C57BL/6J mice. 9–10 weeks (young group) or 44–52 weeks (middle-aged group) exposed to 2 days of constant darkness		15% (214 proteins) displayed circadian rhythms in abundance in the hippocampus of young mice, while only 1.6% (23 proteins) were rhythmic in middle-aged mice Aging disrupts the circadian regulation of proteins involved in cellular functions critical for hippocampal function and memory	[87]
Focal-cerebral ischemia in male SD rats	NREM sleep duration was greater during the dark period but lower during the light period REM sleep duration following stroke (MCAO group) was significantly lower Wake duration increased during the light and 24-h periods following the stroke Melatonin and exercise in combination improved the sleep disruption in MCAO mice	Neurons in the hippocampal CA1 of the MCAO group were lost, atrophied, or loosely arranged PSD was significantly thinner following the stroke Combining melatonin and exercise improved the hippocampal neuroplasticity changes	[91]
Traumatic brain injury in CD-1 mice	Disrupted sleep homeostatic drive	Reduced the amplitude and frequency of mIPSCs in dentate granule cells Dual orexin antagonist (DORA-22) rescued	[90]

Table 2. Continued.

Animal model/clinical study	Effect on sleep/Effect of disease model on sleep	Changes in hippocampal neuroplasticity	Reference
TBI in C57BL/6 mice + sleep fragmentation	Post-injury sleep fragmentation causes deficits in trace fear conditioning acquisition consistent with compromised dorsal hippocampus function	Sleep fragmentation increases cortical inflammation after TBI Sleep fragmentation induced hippocampal CA1 neuronal activity Post-TBI sleep fragmentation enhances ipsilateral CA1 microglia reactivity and imbalanced neuronal activity 30 DPI Post-TBI sleep fragmentation causes persistent microgliosis lateral to the lesion area associated with increased cortical expression of glial pro-inflammatory signaling genes 30 DPI Injury and sleep fragmentation induced Schaffer collateral deficits 30 DPI	[92]
Imaging, behavioral, and genetic datasets of 1200 participants in the age range of 22–35 years		Female good sleepers exhibited larger GMV in the right parahippocampal gyrus extending to the right hippocampus than female poor sleepers Smaller GMV in the right parahippocampal gyrus in women with poor sleep quality	[88]
Forty right-handed, healthy, adult male volunteers		Morning-to-evening increases were observed in cerebral blood flow. A night of sleep deprivation was associated with further cerebral blood flow increases.	[89]
Eighty older adults (aged ≥ 65 years) with first-time TBI >3 months since injury and 80 older adults controls without TBI	Older adults with TBI showed a higher prevalence of OSA, insomnia, and daytime sleepiness than older adult controls.		[93]
Older adults diagnosed with TBI between 2008–2014 (n = 78,044) and non-TBI controls (n = 76,107)	TBI was associated with an increased risk of insomnia		[94]

Abbreviations: 3-MST, 3-mercaptopyruvate sulfurtransferase; AD, Alzheimer's disease; BDNF, brain derived neurotrophic factor; BDPP, bioactive dietary polyphenol preparation; CA, cornu ammonis; CBS, cystathionine β -synthase; CRD, circadian rhythm disorder; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; DEGs, differentially expressed genes; DORA, dual orexin antagonist; DPI, days post-injury; ERK, extracellular signal-regulated kinase; GMV, gray matter volume; IL, interleukin; LTP, long-term potentiation; MCAO, middle cerebral artery occlusion; mIPSCs, miniature inhibitory synaptic currents; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor κ B; NSE, neuron-specific enolase; OPR, object place recognition; OSA, obstructive sleep apnea; PFC, prefrontal cortex; PSD, postsynaptic density; REM, rapid-eye-movement; NREM, non-REM; RSR, REM sleep restriction; SD, Sprague Dawley; SHR, spontaneously hypertensive rat; Syt-1, synaptotagmin 1; TBI, traumatic brain injury; TNF, tumor necrotic factor; WKY, Wistar-Kyoto; ZT, zeitgeber time.

disorders demonstrate decreased cognitive function alongside alterations in hippocampal neuron count and plasticity [64]. However, the direct correlation between circadian rhythm disorders and hippocampal neuroplasticity is not firmly established. Nonetheless, they are considered among several brain regions affected by these disruptions. Consequently, employing specific methodologies aimed at elucidating the precise involvement of the hippocampus in circadian rhythm sleep disorders is warranted. The findings could potentially shed light on the relationship. Furthermore, clarifying this connection could offer valuable insights into the underlying mechanisms of these disorders, thereby potentially guiding informed targeted therapeutic interventions.

3. Hippocampal Function and Neuroplasticity in Sleep Deprivation

While the classifications of sleep disorders delineated in the preceding chapter are consistently observed in human studies, attempts to emulate these conditions in preclinical animal models are often based on sleep disorders induced by sleep deprivation. Sleep deprivation, which is characterized by prolonged periods of inadequate sleep [70], is a primary method to evoke various sleep disturbances, as elucidated and discussed in the preceding chapter. Table 2 (Ref. [64,71–97]) provides a detailed overview of recent research investigating alterations in hippocampal function and neuroplasticity across various sleep disorders and normal sleep-wake cycles. This chapter is divided into three distinct subchapters, with each focusing on a specific aspect of the interplay between hippocampal function and sleep disruptions. This structural setup aims to provide improved comprehensive insight into the hippocampal function and neuroplasticity effect on varying sleep disorders, encompassing various life stages and clinical conditions.

3.1 Maternal Sleep Deprivation and Offspring Hippocampal Function

The central nervous system undergoes critical developmental phases during intrauterine development growth. It is highly vulnerable to maternal sleep deprivation and other external influencing factors [98]. Recent reviews highlight various neurological and non-neurological effects of maternal sleep deprivation on their offspring [99,100]. From these reviews and recent research, maternal sleep deprivation is shown to affect hippocampus-dependent function adversely and synaptic plasticity in offspring, especially in animal models (rodents). Maternal sleep deprivation is linked to cognitive decline [71–74], emotional dysfunction, including depression- or anxiety-like behavior [71–73], and delayed maturation in the sleep-wake neural networks [75].

Additionally, maternal sleep deprivation is associated with linked to reduced levels of brain-derived neurotrophic factor, postsynaptic density protein 95, and

other neuroplasticity-related proteins [72–74], alongside increased hippocampal-proinflammatory cytokine levels [73]. Furthermore, environmental enrichment has shown promise in reversing neurocognitive dysfunction and restoring synaptic protein expression in most of the studies mentioned above [72–74]. Overall, these findings underscore the substantial effect of maternal sleep deprivation on hippocampal function and neuroplasticity in offspring. Furthermore, these findings suggest the potential of environmental enrichment as a therapeutic intervention strategy to mitigate these adverse effects. However, a substantial gap exists in understanding the mechanisms underlying maternal sleep deprivation-induced hippocampal dysfunction in offspring. Thus, further studies are warranted to explore the molecular mechanisms underlying the observed maternal sleep deprivation effect on the hippocampal function of offspring and explore additional intervention and prevention strategies to protect offspring neurodevelopmental outcomes effectively.

3.2 Adulthood Sleep Deprivation and Hippocampal Dysfunction

Several preclinical studies have examined the influence of sleep deprivation in adulthood. For example, mice deprived of sleep displayed depression-like behavior [76] and experienced reduced contextual memory, while their cued memory remained unaffected [77]. Furthermore, sleep deprivation impaired object place recognition and cognitive function in young adult mice [78,79] and rats [80]. Moreover, it enhanced cognitive performance in old mice [79]. The extinction of conditioned fear influenced sleep-deprived rats, while the acquisition of fear conditioning remained unaffected [81].

Further mechanistic studies are crucial to understanding how sleep deprivation leads to hippocampal dysfunction. Transcriptome profiling of the hippocampus in sleep-deprived mice revealed an increase in genes related to RNA splicing and a decrease in genes associated with cell adhesion, dendritic localization, and synaptic membrane function [82]. A total of 16 common differentially expressed genes exhibited similar patterns of change in both sleep-deprived mice and Alzheimer's disease model mice [83]. Sleep deprivation resulted in decreased expression levels of neurotrophic factors and increased cytokine expression in the hippocampus [76,84], suggesting that sleep deprivation adversely affects hippocampal neuronal function through various signaling pathways. Additionally, sleep deprivation impaired cyclic adenosine monophosphate (cAMP) response element-binding protein activation and mammalian target of rapamycin (mTOR) signaling pathways [77]. Moreover, simulated night shift work in rats disrupted pathways that regulate the circadian cycle [85]. Synaptic concentrations of Shank3 protein displayed minor oscillations during the day in hippocampal and striatal brain regions, correlating with changes in serum melatonin

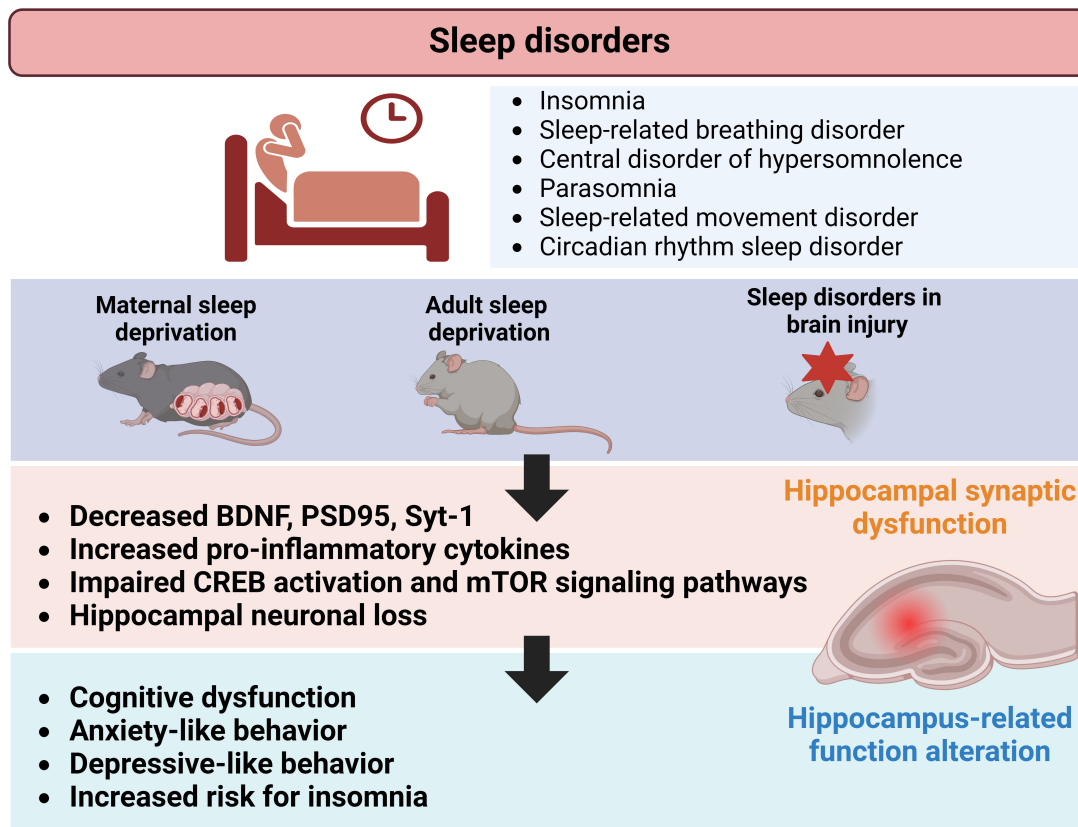


Fig. 1. Schematic illustration depicting alterations in hippocampal neuroplasticity associated with sleep disorders. Preclinical studies investigating maternal-, adult-sleep deprivation, and brain injuries, revealed changes in synaptic proteins, neuronal growth factors, and signaling mechanisms within the hippocampus. These changes may contribute to functional and behavioral alterations, such as neurocognitive dysfunction, observed in individuals affected by sleep disorders. Figure created using BioRender.com (<https://www.biorender.com/>). BDNF, brain derived neurotrophic factor; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; PSD, postsynaptic density; Syt-1, synaptotagmin 1.

levels in mice [86]. It appears that aging disrupts circadian patterns of protein expression in the murine hippocampus. In young mice, 15% (214 proteins) exhibited circadian rhythms in abundance, while only 1.6% (23 proteins) displayed rhythmic in middle-aged mice [87].

Clinical studies suggest that females with good sleep exhibit a larger gray matter volume in the right parahippocampal gyrus than females without good sleep [88]. Additionally, a study involving 40 healthy adult males revealed morning-to-evening increases in cerebral blood flow, with a night of sleep deprivation associated with further increases in cerebral blood flow [89]. However, there is limited information on the hippocampal effects of sleep deprivation in adults than in preclinical studies. Thus, clinical researchers must focus more on improving and stabilizing the current understanding gained from preclinical research. Consequently, the multifaceted influence of sleep deprivation in adulthood on hippocampal function emphasizes the urgent need for additional preclinical/clinical research to clarify its underlying mechanisms and devise targeted interventions to alleviate its detrimental effects on brain health.

3.3 Sleep Disorders in Neurological Disorders

Sleep disorders frequently coexist with varying chronic conditions, including heart disease, kidney disease, high blood pressure, diabetes, obesity, and mental illness [24,101–104]. These disorders may be primary or secondary to other organ and/or nervous system diseases. Consequently, several recent reviews have explored the potential presence of sleep disorders in neurological disorders, such as Parkinson's [105,106] and Alzheimer's disease [105,107–109] and multiple sclerosis [110]. These prevalent neurological disorders are linked to disruptions in hippocampal neuroplasticity at different stages of the disease progression [15,111–114]. Considering the involvement of various brain regions in the pathology of neurological disorders, it is probable that sleep disorders in these conditions result from a combination of mechanisms across multiple brain regions. Moreover, therapeutic interventions administered during the course of neurological disorders have been implicated in sleep disorder development [109].

Additionally, sleep disorders frequently occur after traumatic brain injury (TBI), including conditions such as narcolepsy, posttraumatic hypersomnia, periodic limb movements in sleep, and especially obstructive sleep apnea, which can lead to significant consequences [115–117]. Preclinical animal models of TBI and ischemic stroke have shown disturbances in the sleep homeostatic drive [90,91]. TBI has been demonstrated to decrease the amplitude and frequency of miniature inhibitory synaptic currents in dentate granule cells [90], while sleep fragmentation has been associated with heightened cortical inflammation and hippocampal cornu ammonis 1 neuronal activity post-TBI [92]. Multiple factors probably play a role in the development of sleep disturbances post-TBI. Diffuse axonal injury, for instance, can result in damage to sleep-regulating structures [118]. While direct evidence of hippocampal involvement in sleep disorders following TBI or ischemic stroke is lacking, the hippocampus may be one of the brain regions affected by these injuries [119,120]. Clinical study findings corroborate preclinical evidence, suggesting a connection between TBI and sleep disorders. For instance, older adults with TBI demonstrate a higher prevalence of obstructive sleep apnea, insomnia, and daytime sleepiness than older adult controls [93]. A comprehensive database study showed that TBI was linked to an elevated risk of insomnia [94].

In summary, the presence of sleep disorders alongside neurological conditions highlights the complex relationship between sleep and brain health, necessitating comprehensive clinical management strategies. Further exploration of the molecular mechanisms connecting sleep disorders with neurological conditions, including the distinct role of the hippocampus, is crucial for enhancing our understanding and devising targeted interventions to enhance patient outcomes.

4. Conclusions

Sleep disorders, which have been tested on preclinical setting as maternal sleep deprivation, significantly affect hippocampus-dependent behaviors, such as learning, memory, anxiety, and depression. These behavioral alterations often co-occur with disruptions in hippocampal neuroplasticity (Fig. 1). This review highlights a scarcity of preclinical research examining hippocampal-structural neuroplasticity, particularly regarding specific categories of sleep disorders that are described and defined in human setting. Additionally, inconsistencies exist in the assessment strategies for hippocampal dysfunction during sleep disorders. While sleep dysregulation is also observed in animal models of brain injuries, the direct role of the hippocampus in these injuries remains uncertain owing to widespread damage across multiple brain regions. Nonetheless, molecular and synaptic changes resulting from brain injuries contribute to associated sleep dysregulation, involving various brain regions in the process. This review offers an updated

overview of studies that evaluated hippocampal involvement in sleep disorders and sleep deprivation while highlighting existing gaps in comprehending hippocampal function in this context. Ultimately, this insight may stimulate future mechanistic and therapeutic research efforts in the field.

Author Contributions

PDEWM and CM conceptualized and designed the literature review. Both authors collected the literature. Both authors were involved in paper topic selection, reviewing, and editing. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Poornima D. E. Weerasinghe-Mudiyanselage is serving as one of the Guest editors of this journal. Changjong Moon is serving as one of the Editorial Board members and Guest editors of this journal. We declare that Poornima D. E. Weerasinghe-Mudiyanselage and Changjong Moon have no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Luigi De Gennaro.

References

- [1] Morgan D, Tsai SC. Sleep and the endocrine system. *Critical Care Clinics*. 2015; 31: 403–418.
- [2] Briançon-Marjollet A, Weiszenstein M, Henri M, Thomas A, Godin-Ribuot D, Polak J. The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. *Diabetology & Metabolic Syndrome*. 2015; 7: 25.
- [3] Krause AJ, Simon EB, Mander BA, Greer SM, Saletin JM, Goldstein-Pickarski AN, *et al*. The sleep-deprived human brain. *Nature Reviews. Neuroscience*. 2017; 18: 404–418.
- [4] Graven SN, Browne JV. Sleep and brain development: the critical role of sleep in fetal and early neonatal brain development. *Newborn and Infant Nursing Reviews*. 2008; 8: 173–179.
- [5] Galván A. The Need for Sleep in the Adolescent Brain. *Trends in Cognitive Sciences*. 2020; 24: 79–89.
- [6] Mutti C, Misirocchi F, Zilioli A, Rausa F, Pizzarotti S, Spallazzi

- M, *et al.* Sleep and brain evolution across the human lifespan: A mutual embrace. *Frontiers in Network Physiology*. 2022; 2: 938012.
- [7] Jiang F. Sleep and Early Brain Development. *Annals of Nutrition & Metabolism*. 2019; 75: 44–54.
- [8] Thorpy MJ. Classification of sleep disorders. *Neurotherapeutics*. 2012; 9: 687–701.
- [9] K Pavlova M, Latreille V. Sleep Disorders. *The American Journal of Medicine*. 2019; 132: 292–299.
- [10] Luca A, Luca M, Calandra C. Sleep disorders and depression: brief review of the literature, case report, and nonpharmacologic interventions for depression. *Clinical Interventions in Aging*. 2013; 8: 1033–1039.
- [11] Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. *Sleep Medicine Reviews*. 2001; 5: 423–445.
- [12] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989; 262: 1479–1484.
- [13] Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues in Clinical Neuroscience*. 2008; 10: 329–336.
- [14] Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, Rodríguez-Moreno CB, Trinchero MF, Cafini F, *et al.* Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. *Science*. 2021; 374: 1106–1113.
- [15] Weerasinghe-Mudiyanselage PDE, Ang MJ, Kang S, Kim JS, Moon C. Structural Plasticity of the Hippocampus in Neurodegenerative Diseases. *International Journal of Molecular Sciences*. 2022; 23: 3349.
- [16] Ryan SM, Nolan YM. Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: can exercise compensate? *Neuroscience and Biobehavioral Reviews*. 2016; 61: 121–131.
- [17] Rocca MA, Barkhof F, De Luca J, Frisén J, Geurts JGG, Hulst HE, *et al.* The hippocampus in multiple sclerosis. *The Lancet. Neurology*. 2018; 17: 918–926.
- [18] Jorge RE, Acion L, Starkstein SE, Magnotta V. Hippocampal volume and mood disorders after traumatic brain injury. *Biological Psychiatry*. 2007; 62: 332–338.
- [19] Raven F, Van der Zee EA, Meerlo P, Havekes R. The role of sleep in regulating structural plasticity and synaptic strength: Implications for memory and cognitive function. *Sleep Medicine Reviews*. 2018; 39: 3–11.
- [20] Dijk DJ. Regulation and functional correlates of slow wave sleep. *Journal of Clinical Sleep Medicine*. 2009; 5: S6–S15.
- [21] Watson BO, Buzsáki G. Sleep, Memory & Brain Rhythms. *Daedalus*. 2015; 144: 67–82.
- [22] Buzsáki G, Silva FLD. High frequency oscillations in the intact brain. *Progress in Neurobiology*. 2012; 98: 241–249.
- [23] Karlsson MP, Frank LM. Awake replay of remote experiences in the hippocampus. *Nature Neuroscience*. 2009; 12: 913–918.
- [24] Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience*. 2009; 12: 1222–1223.
- [25] Sirota A, Buzsáki G. Interaction between neocortical and hippocampal networks via slow oscillations. *Thalamus & Related Systems*. 2005; 3: 245–259.
- [26] Hahn TTG, Sakmann B, Mehta MR. Differential responses of hippocampal subfields to cortical up-down states. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104: 5169–5174.
- [27] Miller BR, Hen R. The current state of the neurogenic theory of depression and anxiety. *Current Opinion in Neurobiology*. 2015; 30: 51–58.
- [28] Aimone JB, Li Y, Lee SW, Clemenson GD, Deng W, Gage FH. Regulation and function of adult neurogenesis: from genes to cognition. *Physiological Reviews*. 2014; 94: 991–1026.
- [29] Navarro-Sanchis C, Brock O, Winsky-Sommerer R, Thuret S. Modulation of Adult Hippocampal Neurogenesis by Sleep: Impact on Mental Health. *Frontiers in Neural Circuits*. 2017; 11: 74.
- [30] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014; 146: 1387–1394.
- [31] Rémi J, Pollmächer T, Spiegelhalter K, Trenkwalder C, Young P. Sleep-Related Disorders in Neurology and Psychiatry. *Deutsches Arzteblatt International*. 2019; 116: 681–688.
- [32] WHO. International classification of diseases for oncology (ICD-O). World Health Organization: Switzerland. 2013.
- [33] Araújo T, Jarrin DC, Leanza Y, Vallières A, Morin CM. Qualitative studies of insomnia: Current state of knowledge in the field. *Sleep Medicine Reviews*. 2017; 31: 58–69.
- [34] Rosenberg RP, Benca R, Doghramji P, Roth T. A 2023 Update on Managing Insomnia in Primary Care: Insights From an Expert Consensus Group. *The Primary Care Companion for CNS Disorders*. 2023; 25: 22nr03385.
- [35] Roach M, Juday T, Tuly R, Chou JW, Jena AB, Doghramji PP. Challenges and opportunities in insomnia disorder. *The International Journal of Neuroscience*. 2021; 131: 1058–1065.
- [36] Morin CM, Jarrin DC, Ivers H, Mérette C, LeBlanc M, Savard J. Incidence, Persistence, and Remission Rates of Insomnia Over 5 Years. *JAMA Network Open*. 2020; 3: e2018782.
- [37] Joo EY, Kim H, Suh S, Hong SB. Hippocampal substructural vulnerability to sleep disturbance and cognitive impairment in patients with chronic primary insomnia: magnetic resonance imaging morphometry. *Sleep*. 2014; 37: 1189–1198.
- [38] Riemann D, Voderholzer U, Spiegelhalter K, Hornyak M, Buysse DJ, Nissen C, *et al.* Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. *Sleep*. 2007; 30: 955–958.
- [39] Koo DL, Shin JH, Lim JS, Seong JK, Joo EY. Changes in subcortical shape and cognitive function in patients with chronic insomnia. *Sleep Medicine*. 2017; 35: 23–26.
- [40] Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D, *et al.* The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. *Journal of Clinical Neurology*. 2012; 8: 130–138.
- [41] Winkelman JW, Benson KL, Buxton OM, Lyoo IK, Yoon S, O'Connor S, *et al.* Lack of hippocampal volume differences in primary insomnia and good sleeper controls: an MRI volumetric study at 3 Tesla. *Sleep Medicine*. 2010; 11: 576–582.
- [42] Selim B, Ramar K. Sleep-Related Breathing Disorders: When CPAP Is Not Enough. *Neurotherapeutics*. 2021; 18: 81–90.
- [43] Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. *The European Respiratory Journal*. 2021; 57: 2002258.
- [44] Harper RM, Kumar R, Ogren JA, Macey PM. Sleep-disordered breathing: effects on brain structure and function. *Respiratory Physiology & Neurobiology*. 2013; 188: 383–391.
- [45] Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. *Progress in Brain Research*. 2011; 190: 53–68.
- [46] Halbower AC, Degaonkar M, Barker PB, Earley CJ, Marcus CL, Smith PL, *et al.* Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Medicine*. 2006; 3: e301.
- [47] Trotti LM. Central Disorders of Hypersomnolence. *Continuum*. 2020; 26: 890–907.
- [48] Kamba M, Inoue Y, Higami S, Suto Y, Ogawa T, Chen W. Cerebral metabolic impairment in patients with obstructive sleep apnoea: an independent association of obstructive sleep apnoea with white matter change. *Journal of Neurology, Neurosurgery,*

and Psychiatry. 2001; 71: 334–339.

- [49] Filardi M, D'Anselmo A, Agnoli S, Rubaltelli E, Mastria S, Mangiaruga A, *et al.* Cognitive dysfunction in central disorders of hypersomnolence: A systematic review. *Sleep Medicine Reviews*. 2021; 59: 101510.
- [50] Huang YS, Hsiao IT, Liu FY, Hwang FM, Lin KL, Huang WC, *et al.* Neurocognition, sleep, and PET findings in type 2 vs type 1 narcolepsy. *Neurology*. 2018; 90: e1478–e1487.
- [51] Kim H, Suh S, Joo EY, Hong SB. Morphological alterations in amygdalo-hippocampal substructures in narcolepsy patients with cataplexy. *Brain Imaging and Behavior*. 2016; 10: 984–994.
- [52] Guilleminault C, Kisisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. *Sleep Medicine*. 2006; 7: 163–170.
- [53] Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009; 72: 1296–1300.
- [54] Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valdeoriola F, *et al.* Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *The Lancet. Neurology*. 2006; 5: 572–577.
- [55] Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron*. 2010; 68: 1023–1042.
- [56] Vetrivelan R, Bandaru SS. Neural Control of REM Sleep and Motor Atonia: Current Perspectives. *Current Neurology and Neuroscience Reports*. 2023; 23: 907–923.
- [57] Merlino G, Gigli GL. Sleep-related movement disorders. *Neurological Sciences*. 2012; 33: 491–513.
- [58] Mogavero MP, Mezzapesa DM, Savarese M, DelRosso LM, Lanza G, Ferri R. Morphological analysis of the brain subcortical gray structures in restless legs syndrome. *Sleep Medicine*. 2021; 88: 74–80.
- [59] Rizzo G, Plazzi G. Neuroimaging Applications in Restless Legs Syndrome. *International Review of Neurobiology*. 2018; 143: 31–64.
- [60] Szentkirályi A, Hermesdorf M, Sundermann B, Czira M, Teismann H, Wulms N, *et al.* Periodic limb movements in sleep are linked to decreased hippocampus and amygdala volumes in the population-based BiDirect Study. *Sleep*. 2023; 46: zsac263.
- [61] Kim JH, Duffy JF. Circadian Rhythm Sleep-Wake Disorders in Older Adults. *Sleep Medicine Clinics*. 2018; 13: 39–50.
- [62] Smarr BL, Jennings KJ, Driscoll JR, Kriegsfeld LJ. A time to remember: the role of circadian clocks in learning and memory. *Behavioral Neuroscience*. 2014; 128: 283–303.
- [63] He Y, Cornelissen-Guillaume GG, He J, Kastin AJ, Harrison LM, Pan W. Circadian rhythm of autophagy proteins in hippocampus is blunted by sleep fragmentation. *Chronobiology International*. 2016; 33: 553–560.
- [64] Wang Y, Zhang Y, Wang W, Liu X, Chi Y, Lei J, *et al.* Effects of circadian rhythm disorder on the hippocampus of SHR and WKY rats. *Neurobiology of Learning and Memory*. 2020; 168: 107141.
- [65] Snider KH, Sullivan KA, Obrietan K. Circadian Regulation of Hippocampal-Dependent Memory: Circuits, Synapses, and Molecular Mechanisms. *Neural Plasticity*. 2018; 2018: 7292540.
- [66] Ruby NF. Suppression of Circadian Timing and Its Impact on the Hippocampus. *Frontiers in Neuroscience*. 2021; 15: 642376.
- [67] Eckel-Mahan KL. Circadian Oscillations within the Hippocampus Support Memory Formation and Persistence. *Frontiers in Molecular Neuroscience*. 2012; 5: 46.
- [68] Steele TA, St Louis EK, Videnovic A, Auger RR. Circadian Rhythm Sleep-Wake Disorders: a Contemporary Review of Neurobiology, Treatment, and Dysregulation in Neurodegenerative Disease. *Neurotherapeutics*. 2021; 18: 53–74.
- [69] Xia Z, Storm D. Role of circadian rhythm and REM sleep for memory consolidation. *Neuroscience Research*. 2017; 118: 13–20.
- [70] Abrams RM. Sleep Deprivation. *Obstetrics and Gynecology Clinics of North America*. 2015; 42: 493–506.
- [71] Wei RM, Zhang YM, Li Y, Wu QT, Wang YT, Li XY, *et al.* Altered cognition and anxiety in adolescent offspring whose mothers underwent different-pattern maternal sleep deprivation, and cognition link to hippocampal expressions of *Bdnf* and *Syt-1*. *Frontiers in Behavioral Neuroscience*. 2022; 16: 1066725.
- [72] Zhang YM, Cheng YZ, Wang YT, Wei RM, Ge YJ, Kong XY, *et al.* Environmental Enrichment Reverses Maternal Sleep Deprivation-Induced Anxiety-Like Behavior and Cognitive Impairment in CD-1 Mice. *Frontiers in Behavioral Neuroscience*. 2022; 16: 943900.
- [73] Zhang YM, Wei RM, Li XY, Feng YZ, Zhang KX, Ge YJ, *et al.* Long-term environmental enrichment overcomes depression, learning, and memory impairment in elderly CD-1 mice with maternal sleep deprivation exposure. *Frontiers in Aging Neuroscience*. 2023; 15: 1177250.
- [74] Zhang YM, Wei RM, Ni MZ, Wu QT, Li Y, Ge YJ, *et al.* An enriched environment improves maternal sleep deprivation-induced cognitive deficits and synaptic plasticity via hippocampal histone acetylation. *Brain and Behavior*. 2023; 13: e3018.
- [75] Aswathy BS, Kumar VM, Gulia KK. The effects of rapid eye movement sleep deprivation during late pregnancy on newborns' sleep. *Journal of Sleep Research*. 2018; 27: 197–205.
- [76] Jee HJ, Ryu D, Kim S, Yeon SH, Son RH, Hwang SH, *et al.* Fermented *Perilla frutescens* Ameliorates Depression-like Behavior in Sleep-Deprivation-Induced Stress Model. *International Journal of Molecular Sciences*. 2022; 24: 622.
- [77] Zhao W, Wang J, Bi W, Ferruzzi M, Yemul S, Freire D, *et al.* Novel application of brain-targeting polyphenol compounds in sleep deprivation-induced cognitive dysfunction. *Neurochemistry International*. 2015; 89: 191–197.
- [78] Prince TM, Wimmer M, Choi J, Havekes R, Aton S, Abel T. Sleep deprivation during a specific 3-hour time window post-training impairs hippocampal synaptic plasticity and memory. *Neurobiology of Learning and Memory*. 2014; 109: 122–130.
- [79] Yuan RK, Lopez MR, Ramos-Alvarez MM, Normandin ME, Thomas AS, Uygun DS, *et al.* Differential effect of sleep deprivation on place cell representations, sleep architecture, and memory in young and old mice. *Cell Reports*. 2021; 35: 109234.
- [80] Yang SQ, Jiang L, Lan F, Wei HJ, Xie M, Zou W, *et al.* Inhibited Endogenous H₂S Generation and Excessive Autophagy in Hippocampus Contribute to Sleep Deprivation-Induced Cognitive Impairment. *Frontiers in Psychology*. 2019; 10: 53.
- [81] Sun W, Li J, Cui S, Luo L, Huang P, Tang C, *et al.* Sleep Deprivation Disrupts Acquisition of Contextual Fear Extinction by Affecting Circadian Oscillation of Hippocampal-Infralimbic proBDNF. *eNeuro*. 2019; 6: ENEURO.0165-19.2019.
- [82] Gaine ME, Bahl E, Chatterjee S, Michaelson JJ, Abel T, Lyons LC. Altered hippocampal transcriptome dynamics following sleep deprivation. *Molecular Brain*. 2021; 14: 125.
- [83] Wei Y. Comparative transcriptome analysis of the hippocampus from sleep-deprived and Alzheimer's disease mice. *Genetics and Molecular Biology*. 2020; 43: e20190052.
- [84] Zielinski MR, Kim Y, Karpova SA, McCarley RW, Strecker RE, Gerashchenko D. Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. *Neuroscience Letters*. 2014; 580: 27–31.
- [85] Marti AR, Patil S, Mrdalj J, Meerlo P, Skrede S, Pallesen S, *et al.* No Escaping the Rat Race: Simulated Night Shift Work Alters the Time-of-Day Variation in BMAL1 Translational Activity in

- the Prefrontal Cortex. *Frontiers in Neural Circuits*. 2017; 11: 70.
- [86] Sarowar T, Chhabra R, Vilella A, Boeckers TM, Zoli M, Grabrucker AM. Activity and circadian rhythm influence synaptic Shank3 protein levels in mice. *Journal of Neurochemistry*. 2016; 138: 887–895.
- [87] Adler P, Chiang CK, Mayne J, Ning Z, Zhang X, Xu B, *et al*. Aging Disrupts the Circadian Patterns of Protein Expression in the Murine Hippocampus. *Frontiers in Aging Neuroscience*. 2020; 11: 368.
- [88] Neumann N, Lotze M, Domin M. Sex-specific association of poor sleep quality with gray matter volume. *Sleep*. 2020; 43: zsaa035.
- [89] Elvsåshagen T, Mutsaerts HJ, Zak N, Norbom LB, Quraishi SH, Pedersen PØ, *et al*. Cerebral blood flow changes after a day of wake, sleep, and sleep deprivation. *NeuroImage*. 2019; 186: 497–509.
- [90] Konduru SR, Isaacson JR, Lasky DJ, Zhou Z, Rao RK, Vattam SS, *et al*. Dual orexin antagonist normalized sleep homeostatic drive, enhanced GABAergic inhibition, and suppressed seizures after traumatic brain injury. *Sleep*. 2022; 45: zsac238.
- [91] Zhao H, Zhang T, Zhang H, Wang Y, Cheng L. Exercise-with-melatonin therapy improves sleep disorder and motor dysfunction in a rat model of ischemic stroke. *Neural Regeneration Research*. 2024; 19: 1336–1343.
- [92] Tapp ZM, Cornelius S, Oberster A, Kumar JE, Atluri R, Witcher KG, *et al*. Sleep fragmentation engages stress-responsive circuitry, enhances inflammation and compromises hippocampal function following traumatic brain injury. *Experimental Neurology*. 2022; 353: 114058.
- [93] Wei L, Wen YT, Thompson HJ, Liu CY, Su YK, Chen PY, *et al*. Sleep Disturbances Following Traumatic Brain Injury in Older Adults: A Comparison Study. *The Journal of Head Trauma Rehabilitation*. 2020; 35: 288–295.
- [94] Albrecht JS, Wickwire EM. Sleep disturbances among older adults following traumatic brain injury. *International Review of Psychiatry*. 2020; 32: 31–38.
- [95] Datta S, Oliver MD. Cellular and Molecular Mechanisms of REM Sleep Homeostatic Drive: A Plausible Component for Behavioral Plasticity. *Frontiers in Neural Circuits*. 2017; 11: 63.
- [96] Watson NF, Dikmen S, Machamer J, Doherty M, Temkin N. Hypersomnia following traumatic brain injury. *Journal of Clinical Sleep Medicine*. 2007; 3: 363–368.
- [97] Rao V, Spiro J, Vaishnavi S, Rastogi P, Mielke M, Noll K, *et al*. Prevalence and types of sleep disturbances acutely after traumatic brain injury. *Brain Injury*. 2008; 22: 381–386.
- [98] Chang JJ, Pien GW, Duntley SP, Macones GA. Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship? *Sleep Medicine Reviews*. 2010; 14: 107–114.
- [99] Pires GN, Oliveira TB, Mello VFF, Bezerra AG, Leenaars CHC, Ritskes-Hoitinga M, *et al*. Effects of sleep deprivation on maternal behaviour in animal models: A systematic review and meta-analysis. *Journal of Sleep Research*. 2021; 30: e13333.
- [100] Pires GN, Benedetto L, Cortese R, Gozal D, Gulia KK, Kumar VM, *et al*. Effects of sleep modulation during pregnancy in the mother and offspring: Evidences from preclinical research. *Journal of Sleep Research*. 2021; 30: e13135.
- [101] Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. *Annals of the New York Academy of Sciences*. 2008; 1129: 287–304.
- [102] Hirotsu C, Tufik S, Bergamaschi CT, Tenorio NM, Araujo P, Andersen ML. Sleep pattern in an experimental model of chronic kidney disease. *American Journal of Physiology. Renal Physiology*. 2010; 299: F1379–F1388.
- [103] Vijayan VK. Morbidities associated with obstructive sleep apnea. *Expert Review of Respiratory Medicine*. 2012; 6: 557–566.
- [104] Palagini L, Bruno RM, Gemignani A, Baglioni C, Ghiadoni L, Riemann D. Sleep loss and hypertension: a systematic review. *Current Pharmaceutical Design*. 2013; 19: 2409–2419.
- [105] Matsumoto S, Tsunematsu T. Association between Sleep, Alzheimer's, and Parkinson's Disease. *Biology*. 2021; 10: 1127.
- [106] Weerasinghe-Mudiyanselage PDE, Kim JS, Shin T, Moon C. Understanding the spectrum of non-motor symptoms in multiple sclerosis: insights from animal models. *Neural Regeneration Research*. 2024; 19: 84–91.
- [107] Sun YY, Wang Z, Zhou HY, Huang HC. Sleep-Wake Disorders in Alzheimer's Disease: A Review. *ACS Chemical Neuroscience*. 2022; 13: 1467–1478.
- [108] Prodhon AHMSU, Cavestro C, Kamal MA, Islam MA. Melatonin and Sleep Disturbances in Alzheimer's Disease. *CNS & Neurological Disorders Drug Targets*. 2021; 20: 736–754.
- [109] Kuang H, Zhu YG, Zhou ZF, Yang MW, Hong FF, Yang SL. Sleep disorders in Alzheimer's disease: the predictive roles and potential mechanisms. *Neural Regeneration Research*. 2021; 16: 1965–1972.
- [110] Yusuf FL, Wijnands JM, Kingwell E, Zhu F, Evans C, Fisk JD, *et al*. Fatigue, sleep disorders, anaemia and pain in the multiple sclerosis prodrome. *Multiple Sclerosis*. 2021; 27: 290–302.
- [111] Weerasinghe-Mudiyanselage PDE, Kang S, Kim JS, Kim SH, Wang H, Shin T, *et al*. Changes in structural plasticity of hippocampal neurons in an animal model of multiple sclerosis. *Zoological Research*. 2024; 45: 398–414.
- [112] Kim B, Weerasinghe-Mudiyanselage PDE, Ang MJ, Lee J, Kang S, Kim JC, *et al*. Changes in the Neuronal Architecture of the Hippocampus in a 6-Hydroxydopamine-Lesioned Rat Model of Parkinson Disease. *International Neuropsychology Journal*. 2022; 26: S94–S105.
- [113] Weerasinghe-Mudiyanselage PDE, Ang MJ, Wada M, Kim SH, Shin T, Yang M, *et al*. Acute MPTP Treatment Impairs Dendritic Spine Density in the Mouse Hippocampus. *Brain Sciences*. 2021; 11: 833.
- [114] Kim B, Kim JS, Youn B, Moon C. Dopamine depletion alters neuroplasticity-related signaling in the rat hippocampus. *Animal Cells and Systems*. 2023; 27: 436–446.
- [115] Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. Prevalence and consequences of sleep disorders in traumatic brain injury. *Journal of Clinical Sleep Medicine*. 2007; 3: 349–356.
- [116] Verma A, Anand V, Verma NP. Sleep disorders in chronic traumatic brain injury. *Journal of Clinical Sleep Medicine*. 2007; 3: 357–362.
- [117] Mantua J, Grillakis A, Mahfouz SH, Taylor MR, Brager AJ, Yarnell AM, *et al*. A systematic review and meta-analysis of sleep architecture and chronic traumatic brain injury. *Sleep Medicine Reviews*. 2018; 41: 61–77.
- [118] Zhou Y. Abnormal structural and functional hypothalamic connectivity in mild traumatic brain injury. *Journal of Magnetic Resonance Imaging*. 2017; 45: 1105–1112.
- [119] Dal Pozzo V, Crowell B, Briski N, Crockett DP, D'Arcangelo G. Reduced Reelin Expression in the Hippocampus after Traumatic Brain Injury. *Biomolecules*. 2020; 10: 975.
- [120] Redell JB, Maynard ME, Underwood EL, Vita SM, Dash PK, Kobori N. Traumatic brain injury and hippocampal neurogenesis: Functional implications. *Experimental Neurology*. 2020; 331: 113372.